Parkin, PINK1, and DJ-1 form a ubiquitin E3 ligase complex promoting unfolded protein degradation.

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Scientific Abstract:
Mutations in PARKIN, pten-induced putative kinase 1 (PINK1), and DJ-1 are individually linked to autosomal recessive early-onset familial forms of Parkinson disease (PD). Although mutations in these genes lead to the same disease state, the functional relationships between them and how their respective disease-associated mutations cause PD are largely unknown. Here, we show that Parkin, PINK1, and DJ-1 formed a complex (termed PPD complex) to promote ubiquitination and degradation of Parkin substrates, including Parkin itself and Synphilin-1 in neuroblastoma cells and human brain lysates. Genetic ablation of either Pink1 or Dj-1 resulted in reduced ubiquitination of endogenous Parkin as well as decreased degradation and increased accumulation of aberrantly expressed Parkin substrates. Expression of PINK1 enhanced Parkin-mediated degradation of heat shock-induced misfolded protein. In contrast, PD-pathogenic Parkin and PINK1 mutations showed reduced ability to promote degradation of Parkin substrates. This study identified a functional ubiquitin E3 ligase complex consisting of PD-associated Parkin, PINK1, and DJ-1 to promote degradation of un-/misfolded proteins and suggests that their PD-pathogenic mutations impair E3 ligase activity of the complex, which may constitute a mechanism underlying PD pathogenesis.